

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/25793 A3(51) International Patent Classification⁷: **G01N 33/68**,
C07K 14/415, A61P 37/08(21) International Application Number: **PCT/GB00/03760**(22) International Filing Date: **2 October 2000 (02.10.2000)**(25) Filing Language: **English**(26) Publication Language: **English**(30) Priority Data: **9923306.6** 1 October 1999 (01.10.1999) **GB**(71) Applicant (for all designated States except US): **ISIS INNOVATION LIMITED** [GB/GB]; Ewert House, Ewert Place, Oxford OX2 7BZ (GB).

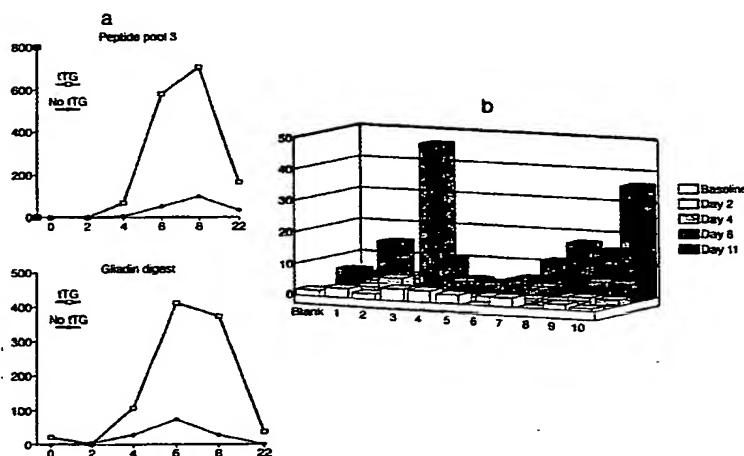
(72) Inventors; and

(75) Inventors/Applicants (for US only): **ANDERSON, Robert, Paul** [GB/GB]; Molecular Immunology, Nuffield Dept of Medicine, Room 7604, Level 7, John RadcliffeHospital, Headington, Oxford OX3 9DU (GB). **HILL, Adrian, Vivian, Sinton** [IE/GB]; Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN (GB). **JEWELL, Derek, Parry** [GB/GB]; Gastroenterology Unit, Gibson Building, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE (GB).(74) Agents: **IRVINE, Jonquil, Claire et al.**; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: **DIAGNOSIS OF COELIAC DISEASE USING A GLIADIN EPITOPE**

(57) Abstract: A method of diagnosing coeliac disease, or susceptibility to coeliac disease, in an individual comprising: (a) contacting a sample from the host with an agent selected from (i) the epitope comprising sequence which is: SEQ ID NO: 1 or 2, or an equivalent sequence from a naturally occurring homologue of the gliadin represented by SEQ ID NO: 3, (ii) an epitope comprising sequence comprising: SEQ ID NO: 1, or an equivalent sequence from a naturally occurring homologue of the gliadin represented by SEQ ID NO: 3, which epitope is an isolated oligopeptide derived from a gliadin protein, (iii) an analogue of (i) or (ii) which is capable of being recognised by a T cell receptor that recognises (i) or (ii), which in the case of a peptide analogue is not more than 50 amino acids in length, or (iv) a product comprising two or more agents as defined in (i), (ii) or (iii), and (b) determining *in vitro* whether T cells in the sample recognise the agent; recognition by the T cells indicating that the individual has, or is susceptible to, coeliac disease. Therapeutic compositions which comprise the epitope and gliadin proteins which do not cause coeliac disease are also provided.



Published:

— with international search report

(88) Date of publication of the international search report:
23 August 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/03760

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/68 C07K14/415 A61P37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, CHEM ABS Data, BIOSIS, EMBASE, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	O'KEEFFE J ET AL: "T cell proliferation, MHC class II restriction and cytokine products of gliadin-stimulated peripheral blood mononuclear cells (PBMC)." CLINICAL AND EXPERIMENTAL IMMUNOLOGY, vol. 117, no. 2, August 1999 (1999-08), pages 269-276, XP000989621 ISSN: 0009-9104 the whole document	1-3, 6-12, 22-26, 37
X	EP 0 905 518 A (UNIV LEIDEN ; ACADEMISCH ZIEKENHUIS LEIDEN (NL)) 31 March 1999 (1999-03-31) the whole document	12, 14-22, 25-59
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

2 March 2001

Date of mailing of the international search report

28/03/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gundlach, B

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/GB 00/03760

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>VAN DE WAL YVONNE ET AL: "Small intestinal T cells of celiac disease patients recognize a natural pepsin fragment of gliadin." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 17, 18 August 1998 (1998-08-18), pages 10050-10054, XP000982626 Aug. 18, 1998 ISSN: 0027-8424 the whole document</p>	1-3, 6-12, 22-26,37
X	<p>TRONCONE R ET AL: "Cytokines produced by gliadin-specific T cell clones from the coeliac mucosa." GASTROENTEROLOGY, vol. 110, no. 4 SUPPL., April 1996 (1996-04), page A1031 XP000989625 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week; San Francisco, California, USA; May 19-22, 1996 ISSN: 0016-5085 abstract</p>	1-3, 6-12, 22-26,37
X	<p>GODKIN A J ET AL: "Identification of a coeliac disease-specific T cell epitope from A-gliadin." GUT, vol. 44, no. SUPPL. 1, April 1999 (1999-04), page A72 XP000989626 British Society of Gastroenterology Annual Meeting; Glasgow, Scotland, UK; March 23-25, 1999 ISSN: 0017-5749 abstract</p>	1-3, 6-12, 22-26,37
A	<p>OKITA T W ET AL: "EVOLUTION AND HETEROGENEITY OF THE ALPHA-BETA-TYPE AND GAMMA-TYPE GLIADIN DNA SEQUENCES" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 260, no. 13, 1985, pages 8203-8213, XP000982597 ISSN: 0021-9258 the whole document -& DATABASE SWISSPROT 'Online! ID: GDA4_Wheat ACC: P04724, 13 August 1987 (1987-08-13) XP002161985 abstract</p>	38-59

-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/03760

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	UHLIG H ET AL: "Role of tissue transglutaminase in gliadin binding to reticular extracellular matrix and relation to coeliac disease autoantibodies." AUTOIMMUNITY, (1998) 28 (4) 185-95. , XP002118954 page 186, left-hand column, paragraph 2 ----	13
P,X	ANDERSON ROBERT P ET AL: "In vivo antigen challenge in celiac disease identifies a single transglutaminase-modified peptide as the dominant A-gliadin T-cell epitope." NATURE MEDICINE, vol. 6, no. 3, March 2000 (2000-03), pages 337-342, XP000982628 ISSN: 1078-8956 the whole document ----	1-34,37
P,X	ARENTZ-HANSEN, HELENE ET AL: "The intestinal T cell response to alpha-gliadin in adult celiac disease is focused on a single deamidated glutamine targeted by tissue transglutaminase" J. EXP. MED., vol. 191, no. 4, 21 February 2000 (2000-02-21), pages 603-612, XP000986723 the whole document -----	1-34,37

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim(s) 5 and 40 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

And although claims 41 and 42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/03760

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0905518 A	31-03-1999	NONE	